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08/607,419

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/607,419	02/28/96	FELDMANN	M KIR92-01A3

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1806	5

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DATE MAILED: 03/04/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-45 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☐ Claim(s) 1-45 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. The filing date of the instant claims is deemed to be the filing date of the instant application USSN 08/607,419, i.e. 2/28/96. Priority application USSN 08/403785 and PCT/GB94/00462 do not support the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "phosphodiesterase inhibitor", "pentoxifylline", "thalidomide", "tumor necrosis factor receptor/immunoglobulin G fusion protein" "preventing Crohn's disease", "tumor factor-mediated disease" and "TNF antagonist" (other than anti-TNF antibodies), "prevents or inhibits tumor necrosis factor synthesis, tumor necrosis factor release of its action on target cells", CD4+ T cell inhibiting agent (other than anti-CD4 antibody). If applicant desires priority prior to 2/28/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Applicant is invited to provide a copy of PCT/GB94/00462, as a copy of said document was not available to the examiner at this time.

3. In the interest of compact prosecution, the examiner has relied in part on an Information Disclosure Statement (1449) cited by the examiner from a copending application.

4. The drawings submitted with this application were declared informal by the applicant. Accordingly, they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review.
Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

The use of trademarks have been noted in this application. A TRADEMARK should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The specification is objected to and claims 1-45 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the clinical treatment of rheumatoid arthritis with multiple infusions with the anti-TNF antibody cA2 and methotrexate for rheumatoid arthritis accurately reflects the relative efficacy of any anti-TNF antibody or anti-TNF specificity as well as targeting any TNF-mediated diseases encompassed by the claimed methods and compositions.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are treated generally after the onset of disease and not prior to disease.

There is insufficient information or guidance as to how to select those patients to "prevent" the onset of the various diseases encompassed by the claimed invention. There is insufficient information to determine which markers would be predictive of said diseases in order to treat patients prior to the onset of said diseases, as a preventive regimen.

Elliott et al. (Arthritis and Rheumatism, 1993) disclose that the appropriate specificity for treating arthritis is TNFα and not TNFβ (see Introduction in particular). Therefore, not all TNFs nor all TNF specificities would be appropriate to target even for the instant exemplified results in arthritis, much less with the breadth of diseases encompassed by the claimed methods. There is insufficient information or nexus for targeting any TNF specificity to treat the breadth of TNF-mediated diseases encompassed by the claimed methods.

Natanson et al. (Ann Int Med., 1994) teach that anti-TNF was not beneficial in sepsis and septic shock, that targeting TNF could be harmful and that TNF fusion proteins have not been successful in vivo (see Anticytokine Therapies).

The specification discloses TNF antagonists such as thalidomide or phosphodiesterase inhibitors such as pentoxifylline; however there is insufficient information or guidance to direct the skilled artisan towards any TNF antagonists. It is not sufficient to define a molecule by its principal biological activity, e.g. TNF antagonists, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. prevents or inhibits TNF synthesis, TNF release or its action on target cells).

Furthermore, there is insufficient guidance and direction as to the selection and enablement of any TNF antagonist.

Therefore, it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions, undue experimentation would be required to practice the claimed methods and compositions with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and compositions and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any TNF-mediated disease and preventing TNF-mediated disease with any TNF-specific antibody.

8. Claims 1-5, 10, 14, 20, 23, 26, 28, 31-32, 35, 40, 43 3, 8, 16, 24, 29 and 31 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-3, 14 are indefinite in the recitation of "tumor necrosis factor-mediated disease" because the characteristics of said diseases are ill-defined and ambiguous. It is not clear whether said diseases reads on any inflammatory condition wherein TNF is present, wherein TNF has a direct role in pathology or wherein TNF has an indirect role in pathology. Although TNF contributes to certain conditions associated with inflammatory diseases, an artisan would not necessarily classify these diseases as TNF-mediated diseases, but rather inflammatory diseases wherein TNF plays some role.

These claims are further ambiguous in the recitation of TNF since there are different members associated with TNF, and it is not clear whether any disease with any role played by any TNF falls into the metes and bounds of "TNF-mediated disease". Applicant should consider amending the claims to specific diseases or inflammatory diseases, where appropriate.

For the reasons set forth above in section 7, there is insufficient guidance and direction as to enable the breadth of treating any TNF specificity in order to treat any "TNF-mediated disease" or inflammatory disease encompassed by the instant claims. In addition, there is insufficient direction and guidance as how to determine whether any TNF or a particular TNF mediates a disease and how critical a role any TNF or a particular TNF has to the diseases encompassed by the claimed invention.

B) Claims 1-5, 10, 14, 20, 23, 26, 28, 31-32, 35, 40, 43 are indefinite in the recitation of TNF "antagonist" and "a receptor molecule which binds to rumor necrosis factor" because their characteristics are not known. This language is vague and indefinite since it encompasses potentially thousands of different antagonists and it is not apparent from the disclosure which particular antagonists or receptor molecules are being referred to. These "antagonists" and "receptor molecules"could be any protein or non-protein molecule that interferes with TNF either in a direct or indirect manner, both known and unknown.

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "antagonists" nor is there evidence provided that such "antagonists" would be effective in inhibiting TNF either in vitro or in vivo, for the reasons set forth above in section 7. It would require undue experimentation to produce all such possible antagonists without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such antagonists. It appears that undue experimentation would be required of one skilled in the art to practice the claimed method using the teaching of the specification alone.

C) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

9. Claims 1-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-45 are indefinite in "tumor necrosis factor" because there are different members of this genus and it is not clear which TNF is intended.

The amendments must be supported by the specification so as not to add any new matter.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-4, 6, 8, 10, , 14-16, 15, 20, 40-41 and 43 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Williams et al. (PNAS, 1994; 1449, #AX). Williams et al. exemplify the use of anti-CD4 and anti-TNF antibodies in the amelioration of established arthritis (see entire document).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced antibodies, compositions thereof and their methods of use.

Since there may be ambiguity over the priority of the instant claims,this rejection is made under 35 U.S.C. § 102(a)(b), as it would apply to the priority of the instant claims if applicant can provide appropriate written support and enablement for the instant or possibly amended claims. See section 2 above concerning priority of the instant claims.

13. Claims 1-45 are rejected under 35 U.S.C. § 103 as being unpatentable over Williams et al. (PNAS, 1994; 1449, #AX), Steinman et al. (U.S. Patent No. 4,695,459), Bender et al. (U.S. Patent No. 5,317,019) and Celltech (WO 92/07585; 1449, AN) in view of Elliott et al. (Arthr. Rheum., 1993; 1449, #AS3), Elliott et al., (Lancet , 1994; 1449, #AT3), Flesch et al. (Blood, 1992), Kay et al. (WO 92/08474; 1449, #AM), Brahn et al. Arthritis Rheum, 1992), Thorbecke et al. (PNAS, 1992), Piguet et al. (Immunol., 1992) and Heinemann et al. (U.S. Patent No. 5,502,066) or Bianco et al. (U.S. Patent No. 5,580,873).

The instant claims are drawn to methods and compositions comprising TNF-nonspecific and specific antagonists in conjunction with CD4-specific antibodies.

Williams et al. exemplify the use of anti-CD4 and anti-TNF antibodies in the amelioration of established arthritis (see entire document).

Steinman et al. teach that anti-CD4 antibodies can be used to treat autoimmune diseases such as rheumatoid arthritis (see entire document). Steinman et al. also teach that the anti-CD4 antibody can be co-administered in humans with antibodies specific to other medical conditions (see column 2, lines 50-54).

Bender et al. teaches the use of TNF antagonists in the treatment of a number of TNF-mediated inflammatory conditions, including arthritis and Crohn's disease encompassed by the claimed methods. Bender et al. differs from the instant claims by not using TNF-specific antibodies and methotrexate to treat said TNF-mediated inflammatory conditions.

Celltech teaches the use of TNF-specific antibodies and xanthine derivatives such as pentoxifylline in the treatment of TNF-mediated inflammation.

Elliott et al. teach the treatment of arthritis with chimeric monoclonal antibodies to TNF, including the instant cA2 specificity (see entire document).

Flesch et al. teaches the treatment of GVHD, which includes a number of lesions including skin and the gut with TNF-specific antibodies (see entire document).

Kay et al. teach the use of CD4-specific antibodies in conjunction with immunosuppressive agents such as cyclosporin as an anti-inflammatory regimen. Although this reference is mostly directed towards the treatment of lung diseases, it does provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition (see entire document).

Markowitz et al. teaches targeting TNF (page 413) and the use of cyclosporin (page 418-419) in the treatment of inflammatory bowel diseases (see entire document)

Brahn et al. teaches the use of cyclosporin to inhibit TNF-mediated arthritis (see Abstract).

Thorbecke et al. and Piguet et al. both teach the use of soluble TNF receptor in the treatment of arthritis (see entire documents).

Heinemann et al. and Bianco et al. both teach the use of other drugs concomitant with the reduction of TNF-mediated disease including thalidomide and xanthine derivatives such as pentoxifylline (see entire document).

The claimed timing of administration and effective dosages were well known in the art, as the ordinary artisan would have applied therapeutic manners to achieve the therapeutic endpoint of diminishing inflammatory conditions.

Therefore, the prior art taught all of the claimed TNF antagonists as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said TNF antagonists to achieve the same desired diminished TNF activity to suit the nature of the therapeutic regimen.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as cyclosporin and xanthine derivatives. Combination therapies were well known in the art and cyclosporin, xanthine derivatives. and anti-inflammatory agent such as TNF-receptors and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 43-57 of copending application Serial No 08/403,785. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to same or similar compositions and methods to treat inflammation, including arthritis and IBD for the reasons above.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-45 are directed to an invention not patentably distinct from claims 43-57 of commonly assigned USSN 08/403,785 because the claims are drawn to same or similar compositions and methods to treat inflammation, including arthritis and IBD for the reasons above.

Commonly assigned 08/403,785, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

17. Claims 1-45 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 08/403,785 in view of other known inhibitors used in the treatment of inflammation, including immunosuppressive agents such as cyclosporin or xanthine derivatives such as pentoxifylline in the treatment of TNF-mediated inflammation as indicated above in section 13.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as cyclosporin and xanthine derivatives. Combination therapies were well known in the art and cyclosporin, xanthine derivatives. and anti-inflammatory agent such as TNF-receptors and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 4, 1997

Phillip Gambel